

**Department of Health and Human Services
National Institute of Environmental Health Sciences
National Cancer Institute**

**Minutes of the State-of-the-Science Subcommittee of the Interagency Breast Cancer and
Environmental Research Coordinating Committee**

April 5, 2011

The State-of-the-Science (SOS) Subcommittee of the Interagency Breast Cancer and Environmental Research Coordinating Committee was convened for a meeting on April 5, 2011 at 2:00 p.m. via conference call. The Chair of the subcommittee is Michele Forman, PhD of the University of Texas M.D. Anderson Cancer Center.

Subcommittee Members Present

Janice Barlow
Suzanne Fenton, PhD
Michele Forman, PhD
Sandra Haslam, PhD
Neeraja Sathyamoorthy, PhD

NIH Staff Present

Jennifer Collins, MR
Heather Shaw, MD

I. BACKGROUND

The Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) is a congressionally mandated body established by the National Institute of Environmental Health Sciences (NIEHS), in collaboration with the National Cancer Institute (NCI). This Committee is comprised of 19 voting members, including representatives of Federal agencies; non-federal scientists, physicians, and other health professionals from clinical, basic, and public health sciences; and advocates for individuals with breast cancer.

The Committee's primary mission is to facilitate the efficient and effective exchange of information on breast cancer research activities among the member agencies, and to advise the NIH and other Federal agencies in the solicitation of proposals for collaborative, multidisciplinary research, including proposals to further evaluate environmental and genomic factors that may be related to the etiology of breast cancer. The Committee serves as a forum and assists in increasing public understanding of the member agencies' activities, programs, policies, and research, and in bringing important matters of interest forward for discussion.

The objectives of the SOS Subcommittee of the IBCERCC are integrated and dependent on the objectives and activities of the other Subcommittees¹ of the IBCERCC and include the following: to summarize the state of the literature (both animal and human research); advances in breast cancer research supported or conducted by Federal agencies relevant to the diagnosis, prevention, and treatment of cancer (and related disorders); and identify research gaps.

¹ The other Subcommittees of the IBCERCC are the Research Process Subcommittee (Chair, Michael Gould) and the Research Translation, Dissemination, and Policy Implications Subcommittee (Chair, Jeanne Rizzo).

The IBCERCC SOS Subcommittee held its third meeting, hosted by NIEHS and the NCI, via webinar on April 5, 2011. Attendees of the meeting included committee members and NIH staff. The meeting agenda included discussion on the following: progress since the last meeting and next steps in addressing the Committee's mandate through the work of this Subcommittee.

II. Discussion

Michele began the meeting but summarizing the progress made during the last meeting on March 29, 2011. She also updated the group on her conversation with Janice regarding the progress section of the report.

Next, Sandy updated the group on the progress made by Sue and her on the summary of the animal research. They spent time fleshing out their outline further. The current outline is as follows:

1. Issue of how to identify which chemicals in environment affect the breast and breast cancer risk
 - a. 80,000+ chems on market and only 1-2% tested
 - b. Out of 2000+ chems tested, 216 affected breast (Rudel et al., 2007)
 1. Identification based on criteria developed by sources cited
 2. Chemicals were identified as carcinogens if at least 1 study increased mammary gland tumors was reported in of the following sources;
 - a. UC Berkeley's Carcinogenic Potency Database (CPDB)
 - b. IARC Monograph Summaries: does not have quality criteria for source material; chemicals carcinogenic in animals present carcinogen hazard in humans
 - c. National Toxicology Program Technical Reports & 11th Report on Carcinogens (11thROC) (2 yr studies). NTP – adult female rats and mice (strain has varied over the years) and control, 3 (high) doses 50 animals per group for 2 years test for tumors in all organs Identified genotoxic agents but not promotional agents
 - d. Chemical Carcinogenesis Research Information System (CCRIS; Nat'l Library of Medicine) (dose (2) route durations, species strain, 25 animals/sex , adequate survival numbers and tumor analysis methods chemical purity)
 3. Sources in the environment:
NLM Hazardous substance database; household products database; ToxNet
EPA's source Ranking Data base, Scorecard Website, Pesticide Action Networks
Pesticide Database, PubChem, Merck Index, Food additives (EAFUS) data base,
Occupational exposure > 5000 women NIOSH
 - c. Chems on market and BC rates still rising (may not be true since there was a decrease after reduction in the use of menopausal HRT). Will report the most up to date data.
2. Animals as a relevant model for breast cancer research
 - a. Similarity of human and rodent mammary gland

- i. Postnatal development of ducts and lobules – include a brief overview of both rodent and human bud development, outgrowth timing. Include the similarity of the glands from different species during “critical periods” of development.)
 - ii. Hormone and growth factor regulation similarities and differences expanded on.
 - iii. Interaction of epithelium and stroma explain that this is a complex gland with 3-4 cell types present at any one time. Makes it hard to target a specific response or cell type to study.
- b. Where do the differences lay – limitations?
 - i. Mouse mammary gland: ductal development occurs prior to pregnancy and lobule development after pregnancy,. There is a difference in progesterone receptor (PR) isoform (PRA<PRB) expression pattern and colocalization in mice compared to humans. Most mammary tumors are ER and PR-negative – however, gene expression profiling indicates that these mouse tumors resemble the luminal type of tumors found in humans and not the basal-like subtype.
 - ii. Rat mammary gland concomitant ducto lobular development prior to pregnancy, progesterone receptor (PR) isoform (PRA, PRB) expression pattern and colocalization and regulation similar to human. Most mammary tumors are ER+PR+ and hormone dependent similar to the majority of human breast cancers

Limitations: neither model is perfect; issues of exposure, agent metabolism, time course of excretion, in vivo half-life; length of lifespan.

3. Search for carcinogens
 - a. Define carcinogen – based on mutagenicity (in vitro assays) or ability to initiate BC in vivo
 - b. Not all chemicals that increase BC risk are carcinogens (can act as promoters subsequent to a mutation/initiating event, endocrine disruptors)
 - c. Identification of the effects of chemical mixtures (Timing/Temporal effects; additive, synergistic, antagonistic effects)
 - d. How measured?
4. NTP research focused on finding carcinogens
 - a. Info about the testing paradigm used (see above)
 - b. Small number of carcinogens ID'd and not all mammary gland (Rudel et al., 2007)
 - c. Problem – mammary gland not always evaluated (Makris – EHP 2010 online)
 - d. Need to define what effects on mammary gland are relevant to BC (issue of fibroadenomas – probably not relevant since FA are not considered precancerous in humans)
 - e. Bigger problem- potential for false negatives
 - f. Strain/species issues
 - i. Rat vs mouse neither model perfect
 - ii. Some strains inappropriate. Some strains of mice are highly resistant to mammary carcinogenesis (C57BL/6) this presents a problem since the majority of gene deletions (oncogenes, tumor suppressors) are generated in this strain. Thus backcrossing to a susceptible strain should be considered.

- iii. Inbred/outbred. Outbred strains, while genetically heterogeneous, may obscure important effects relevant to a specific genetic background. The use of inbred strains overcomes this problem, but may result in other complicating factors (small offspring numbers, poor breeding outcomes). However, overriding effects in outbred strains may indicate a global effect that overcomes differences in genetic background.
 - iv. Therefore, more than one strain/species should be tested
- 5. Critical periods of development (Fenton 2006 Endocrinology)
 - a. In utero and neonatal – alter early MG development and may set the stage for permanent lifetime changes.
 - b. Puberty – exposures during this time period may interact with or alter endogenous hormones and growth factors, can alter timing of pubertal development and subsequent BC suscept.
 - c. Pregnancy – exposures can affect proliferation and lactational differentiation and function. This has implications for child well being and may carryover to neonatal MG devel;
 - d. Exposures that affect MG development during pregnancy may alter (reduce) the potential protective effects of pregnancy
 - e. Changes at any stage of mammary gland development may affect lifelong susceptibility
 - f. Several chemicals ID'd that affect mammary gland development (Rudel et al., 2011)
 - g. estrogenic compounds (pharmaceuticals, phytoestrogens, etc)
 - h. Pesticides
 - i. Other manufactured chemicals
 - j. Others (unclear)
- 6. New lines of investigation – lifelong susceptibility changes
 - a. Endocrine disruption (can affect any local or systemic mechanism that regulates mammary gland development and function; hormones other than estrogen, i.e. other steroid hormones, their synthesis, inactivation, growth factors, inflammatory processes)
 - i. Not carcinogenic by themselves
 - ii. May have stage specific effects
 - iii. Estrogenic effects over emphasized
 - iv. May change lifelong sensitivity to another 'hit' (i.e., carcinogen)
 - v. There are examples of mammary gland as the most sensitive end point assessed (Rudel et al., 2011) – 5 listed, one in males only.
 - b. Developmental reprogramming
 - i. Early life exposures change course of tissue for life
 - ii. Altered receptor expression, altered susceptible cell populations (stem cell/progenitor cells); altered stroma, alterations of non mammary organs and/or tissues that impact mammary gland development (ovary, pituitary, adrenal, immune system etc)
 - iii. Epigenetic changes (gene activation/inactivation)
 - c. How are adverse effects defined – new sentinel events for cancer susceptibility?

- i. Development – permanent effects (ductal morphology, cell populations, gene expression profiles, response to hormones)
 - ii. Lactation impairment (impaired alveogenesis, impaired lactational function)
 - iii. Hyperplasia and potential precursors to neoplasia – early events
- 7. How to move forward?
 - a. Better testing of chemicals and various routes and timing of exposures – changes in 2011 in NTP
 - b. Need to consider new mechanisms of exogenous hormone exposure (sustained birth control treatment, bioidentical menopausal HRT)
 - c. TSCA reform - need to know more about chems before they hit market
 - d. Develop the NCI website on carcinogens - needs an update
 - e. Urgent need for better understanding of reprogramming following early life exposures
 - f. Translational type studies – NIEHS BCERP as example where epidemiological and animal studies are carried out in collaboration to identify exposures in humans, test the effects of the exposures in animal models of mammary development and carcinogenesis and identify potential biomarkers of exposure susceptibility in humans.

The group discussed exposure kinetics, specifically with regard to how long a chemical can be in an individual and in the environment. In order to investigate this, one would have to do a longitudinal NHANES type study, but the exposure could still be missed if it has a short half-life. People are starting to look at combinations of exposures. For risk assessment new tools are needed to assess mixtures. Animals can help with this (can analyze chemicals and in isolation and in combination). This could be part of a recommendation/research gap.

The coverage of adipose tissue was also discussed. Sandy said that this would be considered part of the stroma, but that to this point, stroma is not well examined. Mammogram density is a risk factor but we do not yet have a handle on what constitutes that density.

If something is a known risk factor in humans, then we need to investigate this thoroughly in animal models. For example, the effect of lactational impairment on the offspring needs more investigation. Research suggests that a full lactational development reduces breast cancer risk. If you are not able to reach that point then you might be affecting risk. Can we evaluate those who try to breast feed and fail and those who succeed? One problem with doing this is that the duration of lactation has other additional confounders that do not apply in animals.

The components in breast milk need to be studied. Investigators funded by BCERP are not examining this. It is important to understand factors that are transferred during lactation from the mother to the offspring. Since an infant liver is not fully developed till 6 months after birth, this will determine how chemicals are metabolized.

The group requested that Sue describe some of the proposed NTP changes. She explained that the NTP is including developmental exposures in all cancer bioassays and taking samples of

mammary gland whole mounts in cancer bioassays and other studies (instead of cross section). With these changes, the NTP should be much better equipped to assess/identify mammary gland carcinogens.

More research is needed to assess the fate of chemicals. Information is needed with regard to where chemicals reside in the environment/humans, how long they can reside there, and how they are metabolized (what are their metabolites and are they more/less toxic than the parent compound).

Michele noted that there are many similarities between the two outlines (animal studies, epidemiology studies). She commented that it is going to be interesting to see how these two sets of papers evolve. She asked the group whether they thought that the two sections could be formatted similarly to ensure appropriate coverage by both. This could potentially allow for arrival at recommendations that would be fairly similar.

Michele reported that she has been reading papers since the 2007 papers in order to bring the research to date from that point.

Janice said that Silent Spring has a nine page chart (funded under Avon) listing all the major breast cancer research studies, including the study info along with the environmental chemical tested. She indicated that it was developed with the goal of identifying gaps in environmental areas. It was finished in 2010 and is available on their web site (Janice will send the link.).

Heather provided some information on the portfolio analyses being conducted by the Research Process Subcommittee. She reported that about 10% of the NCI grants and about 100/600 grants covering the rest of NIH deal with either etiology or prevention.

Janice provided an update on the progress section of the report that she is working on with Michele and Heather. The plan is to frame the section to positively answer questions often asked by funding agencies, patients, and the general public:

- Are we really making progress?
- Has anything really changed?
- All that money into research-has it done any good
- How have patients, communities and public health benefited?

They would like to highlight those advances that have affected our current perspectives on tumor biology, treatment, risk and prevention, especially in regard to the role environmental factors play in the initiation and promotion of breast cancer.

One advance proposed is the recognition of the complexity of breast cancer. Janice suggested that the differentiation by gene expression patterns of intrinsic breast cancer subtypes is an advance. Sandy pointed out that this finding has not changed therapy dramatically even though the potential is there. A critical review of what this progress has led to is needed. It is also not known which kind of tumors result from a specific exposure.

The suggestion that both genetic environmental susceptibility differs across subtypes provides an opportunity to reconsider risk. It is entirely possible that modifiable lifestyle factors may be highly relevant in preventing breast cancer in certain populations.

Benefit of physical activity has not been really realized because we get caught up in the inconsistencies in the research. As a result, information is not getting disseminated.

Some drugs point to potential mechanisms (statins, NSAIDs, etc.) – we need a better understanding of the etiology of breast cancer.

Heather presented a summary of all the recent advances (funded by Federal agencies) in breast cancer treatment and prevention from her perspective in the clinic. She included chemotherapies, hormonal therapies, targeted therapies, prevention agents, surgery, risk prediction genetic testing, and imaging. The group suggested that a time line for all of these would be a useful addition to the report that might make gaps apparent.

Sue suggested that it is important for this group to come up with some percent that the environment contributes to breast cancer risk. The group agreed that the best way would be to present the numbers attributable to genetic contributions because even if you use 27%, then that still leaves a lot to potential contributions from the environment. The research advances in genetics have been much more substantial than in environmental research.

This Subcommittee does not have another meeting scheduled until May 10. Michele requested that each group update the Subcommittee on a weekly basis (Tuesdays). Jenny will send an Outlook reminder for this.

Each work group will present to the full Committee on May 12. As such, each group should think about recommendations, what we are missing from the other subcommittees, and resources needed (materials, staff support, etc.). Jenny suggested that template slides would be useful for the groups as they develop their materials. Jenny and Michele will develop a template and distribute to the group.

The group ended with a discussion on the length for each of the sections (animal/epi studies). Sue asked would it 20 pages or 8 pages. Michele indicated that it would be more likely in the 8 page range and that the majority of the effort should be directed toward moving the science forward (not reviewing what has already been done).

Action Items

- Janice will send the link to the Silent Spring chart.
- Heather and Janice will continue to work on the progress section and sent to Michele for review.
- Each group will report progress to the group each Tuesday until the May meeting – Jenny will send an Outlook even out for this.
- Michele and Jenny will draft a template for use in the presentations on May 12.

III. Adjournment

The meeting adjourned at 4:00 p.m. on April 5, 2011.

CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.

/Michele Forman/

Michele Forman, PhD

Chairperson

State-of-the-Science Subcommittee

Interagency Breast Cancer & Environmental Research Coordinating Committee

/Gwen W. Collman/

Gwen W. Collman, PhD

Executive Secretary

Research Process Subcommittee

Interagency Breast Cancer & Environmental Research Coordinating Committee

Proper signatures

Treat as signed, § 1.4(d)(2)